News Release

Title

Dorsal-to-ventral cortical expansion is physically primed by ventral streaming of early embryonic preplate neurons

Key Points

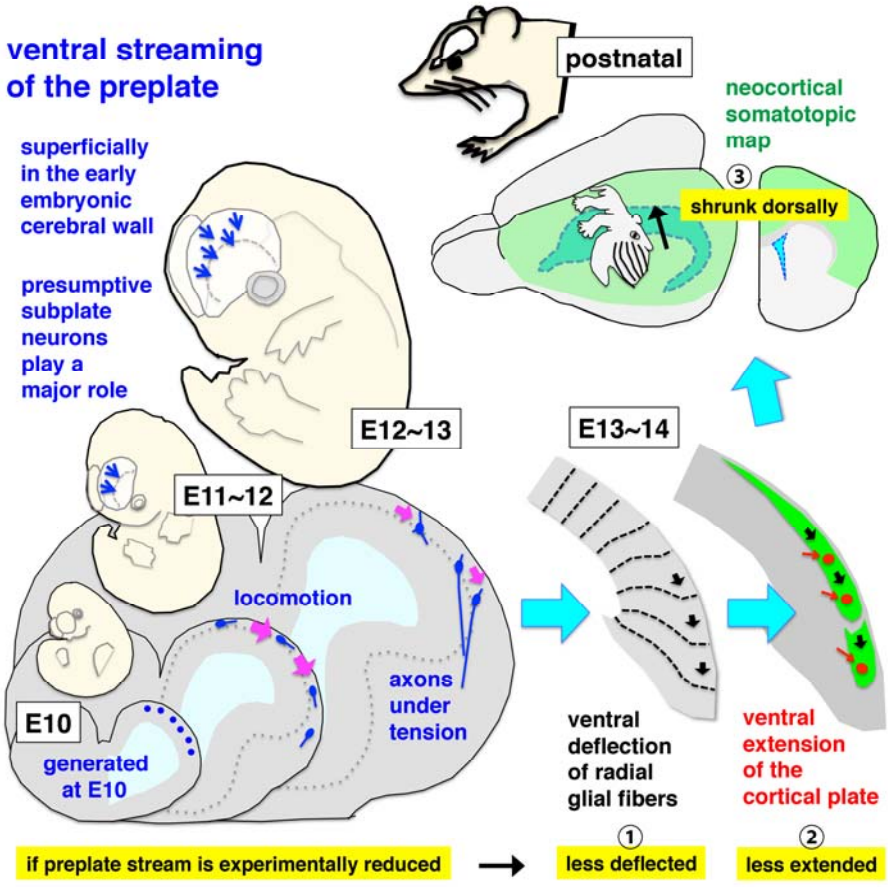
How the embryonic neocortex expands ventrally has not been understood mechanically.

Preplate neurons generated in the earliest corticogenic stage stream ventrally.

Decreasing this stream reduces the normal ventral deflection of radial glial fibers.

Decreasing this stream dorsally shrinks the postnatal neocortical map.

Summary 1



Despite recent studies elucidating the molecular mechanisms underlying cortical patterning and map formation, we know very little about how the embryonic pallium expands ventrally to form the future cortex and the nature of the underlying force-generating events. In the present study, Professor Takaki Miyata, Assistant Professor Kanako Saito, and colleagues in Nagoya University Graduate School of Medicine (dean: Kenji Kadomatsu, M.D., Ph. D.) showed that neurons born at embryonic day 10 (E10) in the mouse dorsal pallium ventrally streamed until E13, thereby superficially spreading the preplate, and then constituted the subplate from E14. From E11 to E12, the preplate neurons migrated exerting pulling and pushing forces at the process and the soma, respectively. At E13, they were morphologically heterogeneous with ~40% possessing corticofugal axons, which were found to be in tension. Ablation of these E10-born neurons attenuated both deflection of radial glial fibers (by E13) and extension of the cortical plate (by E14), which should occur ventrally, and subsequently shrank the postnatal neocortical map dorsally. Thus, the

preplate stream physically primes neocortical expansion and arealization. This study was published online in Cell Reports on November 6, 2019.

Summary 2

Embryonic radial glial fibers that guide most neocortical neurons are ventrally deflected near their terminal, contributing to further expansion of the neocortical area. Saito et al. demonstrate that this fiber deflection is induced physically by a previously unrecognized ventral stream of the earliest-generated preplate neurons

Research Background

Mammalian neocortex exhibits a disproportionally "luxurious" representation of somatotopies in its lateral region. The adult lateral neocortex, where the homunculus or mouseunculus is broadly mapped, is superficial to the striatum. In early embryonic development, by contrast, the pallium (neocortical primordium) is dorsal to the ganglionic eminences (striatal primordia), indicating that the pallium, especially its outer (i.e., neuronal) zone, undergoes ventral expansion/growth in order to "ride on" the striatum. Clonal analyses revealed a greater tangential dispersion of neurons in the lateral part of the growing neocortex than in the medial part. One explanation for this ventral neocortical expansion is that radial glial fibers, which are used for neuronal guidance, exhibit an extensively curving and divergent alignment pattern in the lateral part, which can be coupled with tangential translocations of neurons from one radial fiber (RF) to another. In addition, the fact that neuron production by progenitors begins and proceeds earlier in the lateral/ventral part than in the dorsomedial parts allows us to imagine that tissue volume can easily increase laterally or ventrally. There remains, however, an additional model that has not been previously tested due to technical difficulties: dorsal-to-ventral migration of neurons born very early in the pallium could contribute to the ventral-dominant neocortical expansion, either directly or by causing (rather than resulting from) the curvature of RFs.

Research Results

We performed in utero electroporation of the dorsal pallium at E10, followed by *in vivo* analyses with various survival/chasing time periods, as well as by live imaging in slice cultures. *In vivo* data revealed that most of the E10 dorsal pallium–derived neurons were histologically identified as SP neurons, and that these cells were more ventrally distributed than their VZ origins. Slice cultures provided an explanation for this ventral shift: these presumptive SP neurons streamed ventrally, with an initial (E11–E12) locomotion-like mode of migration and the subsequent (~E13) somal translocation based on their heterogeneous morphologies including the corticofugal axon.

Research Summary and Future Perspective

The neocortex and the striatum are in a dorsal–ventral relationship during the early embryonic primordial period, and in a superficial–deep relationship in the postnatal/adult mammalian cranium. A ventral spreading of the neocortex to externally or superficially cover the striatum (to be worn as a "pallium" [= vestment] by the striatum) is coupled with an inward growth of the striatum to narrow the lateral ventricle. Together, these effects promote space efficiency in the fetal cranium, whose growth is ultimately constrained by the size of

the birth canal. Recent studies revealed that embryonic brains that develop under space limitations are sensitive to the physical conditions faced by their cells during development, and that developing brains utilize physical or mechanical factors that emerge as a function of the morphology, 3D assembly pattern, and behavior of brain-forming cells. In this study, we identified another way in which cells use an externally provided force to fulfill their developmental roles. The asymmetric (ventral-ward) deflection of RFs, which forms the basis for the protomap mechanism underlying the establishment of functional neocortical maps, depends on the ventral streaming of PP neurons (including future SP neurons) born early in the pallium. Further studies with mechanical viewpoints will facilitate the understanding of brain morphogenesis.

Publication

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